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(21) International Application Number: PCT/US96/11807 (22) International Filing Date: 16 July 1996 (16.07.96) (30) Priority Data: 60/001,453 17 July 1995 (17.07.95) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): LIN, Min [CN/US]; 1808 Pheasant Hollow Drive, Plainsboro, NJ 08536 (US). SCHWEISS, Dieter [DE/US]; 320 Blue Isle Drive, Holland, MI 49424 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AU, BG, BR, CA, CN, CZ, EE, GE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, UZ, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: NOVEL PROCESS FOR THE PRODUCTION OF AMORPHOUS [R-(R*.R*)]-2-(4-FLUOROPHENYL)- β , δ -DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID CALCIUM SALT (2:1) (57) Abstract A novel process for the preparation of amorphous atorvastatin is described where crystalline Form I atorvastatin is dissolved in a non-hydroxylic solvent and after removal of the solvent affords amorphous atorvastatin.		

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-1-

5 NOVEL PROCESS FOR THE PRODUCTION OF AMORPHOUS
[R-(R*,R*)]-2-(4-FLUOROPHENYL)- β,δ -DIHYDROXY-5-
(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-
1H-PYRROLE-1-HEPTANOIC ACID CALCIUM SALT (2:1)

10 BACKGROUND OF THE INVENTION

The present invention relates to a novel process
for amorphous atorvastatin which is known by the
chemical name [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -
15 dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)
carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt
which is useful as a pharmaceutical agent.
Atorvastatin is useful as an inhibitor of the enzyme
3-hydroxy-3-methylglutaryl-coenzyme A reductase
20 (HMG-CoA reductase) and is thus useful as a
hypolipidemic and hypocholesterolemic agent.

United States Patent Number 4,681,893, which is
herein incorporated by reference, discloses certain
trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-
25 yl)alkyl]-4-hydroxy-pyran-2-ones including trans (\pm)-5-
(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-
[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-
pyrrole-3-carboxamide.

United States Patent Number 5,273,995, which is
30 herein incorporated by reference, discloses the
enantiomer having the R form of the ring-opened acid of
trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-
diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-
2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e.,
35 [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-
methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-
pyrrole-1-heptanoic acid.

United States Patent Numbers 5,003,080; 5,097,045;
5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174;

-2-

5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

5 Atorvastatin is prepared as its calcium salt, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The calcium salt is desirable since it enables atorvastatin
10 to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration.

 Concurrently filed United States Patent Applications titled "Crystalline [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic Acid Calcium Salt (2:1)" and "Form III Crystalline [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic Acid Calcium Salt (2:1)" commonly
15 owned, attorney's Case Numbers PD-5250-01-FJT, Serial Number _____, and PD-5333-01-FJT, Serial Number _____, disclose atorvastatin in various new crystalline forms designated Form I, Form II, Form III, and
20 Form IV.
25 Form IV.

 Atorvastatin disclosed in the above United States Patents is an amorphous solid. We have found that after the advent of crystalline atorvastatin, the production of amorphous atorvastatin by the previously
30 disclosed processes was not consistently reproducible.

 It has been disclosed that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline
35 form (Konno T., Chem. Pharm. Bull., 1990;38:2003-2007). For some therapeutic indications one bioavailability

-3-

pattern may be favored over another. Therefore, it is desirable to have a procedure for converting the crystalline form of a drug to the amorphous form.

5 The object of the present invention is a process which is amenable to large-scale production for converting crystalline Form I atorvastatin into amorphous atorvastatin.

10 We have surprisingly and unexpectedly found that solutions of atorvastatin in a non-hydroxylic solvent afford, after removal of the solvent, amorphous atorvastatin.

SUMMARY OF THE INVENTION

15

Accordingly, the present invention is a novel process for the preparation of amorphous atorvastatin and hydrates thereof which comprises:

20 (a) dissolving crystalline Form I atorvastatin in a non-hydroxylic solvent; and

(b) removing the solvent to afford amorphous atorvastatin.

25 In a preferred embodiment of the invention, the non-hydroxylic solvent is selected from the group consisting of: tetrahydrofuran, and mixtures of tetrahydrofuran and toluene.

In another preferred embodiment of the invention, the solvent is removed in a vacuum dryer.

30

BRIEF DESCRIPTION OF THE DRAWINGS

35 The invention is further described by the following nonlimiting examples which refer to the accompanying Figures 1, 2, and 3, short particulars of which are given below.

-4-

Figure 1

Diffractionogram of Form I atorvastatin ground for 2 minutes (Y-axis = 0 to maximum intensity of 3767.50 counts per second(cps))

5

Figure 2

Diffractionogram of amorphous atorvastatin (Y-axis = 0 to maximum intensity of 1455.00 cps)

10

Figure 3

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form I atorvastatin.

15

DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form I atorvastatin may be characterized by its X-ray powder diffraction pattern and/or by its solid state nuclear magnetic resonance spectrum (NMR).

20

X-RAY POWDER DIFFRACTION

25

Amorphous and Form I Atorvastatin

Amorphous and Form I atorvastatin were characterized by their X-ray powder diffraction patterns. Thus, the X-ray diffraction patterns of amorphous and Form I atorvastatin were measured on a Siemens D-500 diffractometer with CuK_α radiation.

30

Equipment

Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software = DIFFRAC AT (SOCABIM 1986, 1992).

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-5-

CuK_a radiation (20 mA, 40 kV, $\lambda = 1.5406 \text{ \AA}$) Slits I and II at 1°) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)] Detector (Slits: III at 1° and IV at 0.15°).

5

Methodology

The silicon standard is run each day to check the X-ray tube alignment.

10 Continuous $\theta/2\theta$ coupled scan: 4.00° to 40.00° in 2θ , scan rate of 6°/min: 0.4 sec/0.04° step (scan rate of 3°/min: 0.8 sec/0.04° step for amorphous atorvastatin).

15 Sample tapped out of vial and pressed onto zero-background quartz in aluminum holder. Sample width 13-15 mm (sample width ~16 mm for amorphous atorvastatin).

Samples are stored and run at room temperature.

Grinding

20 Grinding is used to minimize intensity variations for the diffractogram of Form I atorvastatin disclosed herein. However, if grinding significantly altered the diffractogram or increased the amorphous content of the sample, then the diffractogram of the unground sample was used.

25

Table 1 lists the 2θ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >20% for crystalline Form I atorvastatin. Table 1 also lists the relative intensities of the same lines in a diffractogram measured after 2 minutes of grinding. The intensities of the sample ground for 2 minutes are more representative of the diffraction pattern without preferred orientation. It should also be noted that

30

35

-6-

the computer-generated, unrounded numbers are listed in this table.

5 TABLE 1. Intensities and Peak Locations of all
Diffraction Lines With Relative Intensity
Greater Than 20% for Form I Atorvastatin

	2 θ	d	Relative Intensity (>20%)	
			No Grinding	Ground 2 Minutes
	9.150	9.6565	37.42	42.60
	9.470	9.3311	46.81	41.94
10	10.266	8.6098	75.61	55.67
	10.560	8.3705	24.03	29.33
	11.853	7.4601	55.16	41.74
	12.195	7.2518	20.03	24.62
	17.075	5.1887	25.95	60.12
15	19.485	4.5520	89.93	73.59
	21.626	4.1059	100.00	100.00
	21.960	4.0442	58.64	49.44
	22.748	3.9059	36.95	45.85
	23.335	3.8088	31.76	44.72
20	23.734	3.7457	87.55	63.04
	24.438	3.6394	23.14	21.10
	28.915	3.0853	21.59	23.42
	29.234	3.0524	20.45	23.36

25 * The second relative intensity column gives
the relative intensities of the diffraction
lines on the original diffractogram after
2 minutes of grinding.

30 SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

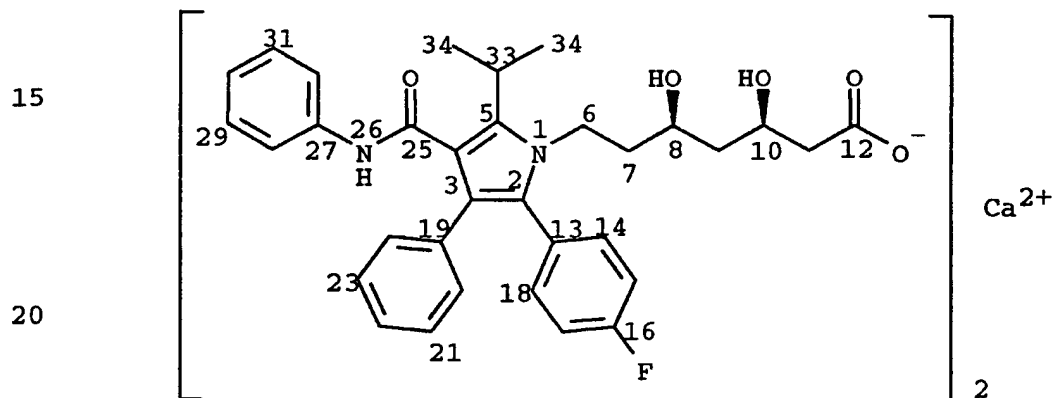
Methodology

35 All solid-state ^{13}C NMR measurements were made
with a Bruker AX-250, 250 MHz NMR spectrometer. High
resolution spectra were obtained using high-power
proton decoupling and cross-polarization (CP) with
magic-angle spinning (MAS) at approximately 5 kHz. The

-7-

magic-angle was adjusted using the Br signal of KBr by detecting the side bands as described by Frye and Maciel (Frye J.S. and Maciel G.E., J. Mag. Res., 1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J.V. and Stock L.M., J. Mag. Res., 1988;76:54).

Table 2 shows the solid-state spectrum for crystalline Form I atorvastatin.



-8-

TABLE 2. Carbon Atom Assignment and Chemical Shift
for Form I Atorvastatin

Assignment (7 kHz)		Chemical Shift
5	C12 or C25	182.8
	C12 or C25	178.4
	C16	166.7 (broad) and 159.3
Aromatic Carbons		
10	C2-C5, C13-C18, C19-C24, C27-C32	137.0
		134.9
		131.1
		129.5
		127.6
15		123.5
		120.9
		118.2
		113.8
20	C8,C10	73.1
		70.5
		68.1
		64.9
Methylene Carbons		
25	C6, C7, C9, C11	47.4
		41.9
		40.2
	C33	26.4
30		25.2
	C34	21.3

Amorphous atorvastatin of the present invention can exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms, are equivalent to

-9-

anhydrous forms and are intended to be encompassed within the scope of the present invention.

As previously described, amorphous atorvastatin is useful as an inhibitor of the enzyme, HMG-CoA
5 reductase and is thus useful as a hypolipidemic and hypocholesterolemic agent.

The present invention provides a process for the commercial preparation of amorphous atorvastatin.

Thus, crystalline Form I atorvastatin is dissolved
10 in a non-hydroxylic solvent such as, for example, tetrahydrofuran, mixtures of tetrahydrofuran and toluene and the like at a concentration of about 25% to about 40%. Preferably, crystalline Form I atorvastatin is dissolved in tetrahydrofuran at a concentration of
15 about 25% to about 40% containing up to about 50% toluene as a co-solvent. The solvent is removed using, for example, drying technology such as, for example, vacuum drying, spray drying, and the like. Preferably, the drying procedure uses an agitated pan dryer such
20 as, for example, Comber Turbodry Vertical Pan Dryer and the like. Drying initially is carried out at about 20°C to about 40°C and subsequently at about 70°C to about 90°C under vacuum at about 5 mm Hg to about 25 mm Hg for about 3 to about 5 days. Preferably,
25 initial drying is carried out at about 35°C and subsequently at about 85°C at about 5 mm Hg to about 25 mm Hg for about 5 days. The initial solution dries to a brittle foam that is broken up by mechanical agitation to afford amorphous atorvastatin.

30 The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

-10-

EXAMPLE 1

[R-(R*,R*)]-2-(4-Fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin)

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48-58°C for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25-35°C, the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47-52°C. To this solution is added a solution of calcium acetate hemihydrate (11.94 kg) dissolved in water (410 L), over at least 30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to 51-57°C for at least 10 minutes and then cooled to 15-40°C. The mixture is filtered, washed with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60-70°C under vacuum for 3 to 4 days to give crystalline Form I atorvastatin (72.2 kg).

EXAMPLE 2

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Amorphous Atorvastatin)

-11-

Crystalline Form I atorvastatin (Example 1) (30 kg) is dissolved with agitation in tetrahydrofuran (75 L) at ambient temperature under a nitrogen atmosphere. Toluene (49.4 L) is added slowly once solution is achieved. The solution is then transferred through a 0.45 micron Pall filter to a 200 L Comber Turbodry Vertical Pan Dryer. The transfer system is rinsed to the dryer with additional tetrahydrofuran (4.5 L). Full vacuum is applied, and the solution is concentrated at 35°C with mild agitation. Near the end of the concentration process, the agitator is lifted. The product turns into a brittle glassy foam. The agitator is gradually lowered, breaking the brittle foam into a free flowing powder. The powder is agitated and the temperature is raised to 85°C under vacuum (6 to 8 mm Hg) to lessen the residual solvent levels. After 4 days of drying, the desired residual solvent levels of 0.01% tetrahydrofuran and 0.29% toluene are achieved. The free flowing white powder (27.2 kg) is unloaded from the dryer. The product is amorphous by X-ray powder diffraction.

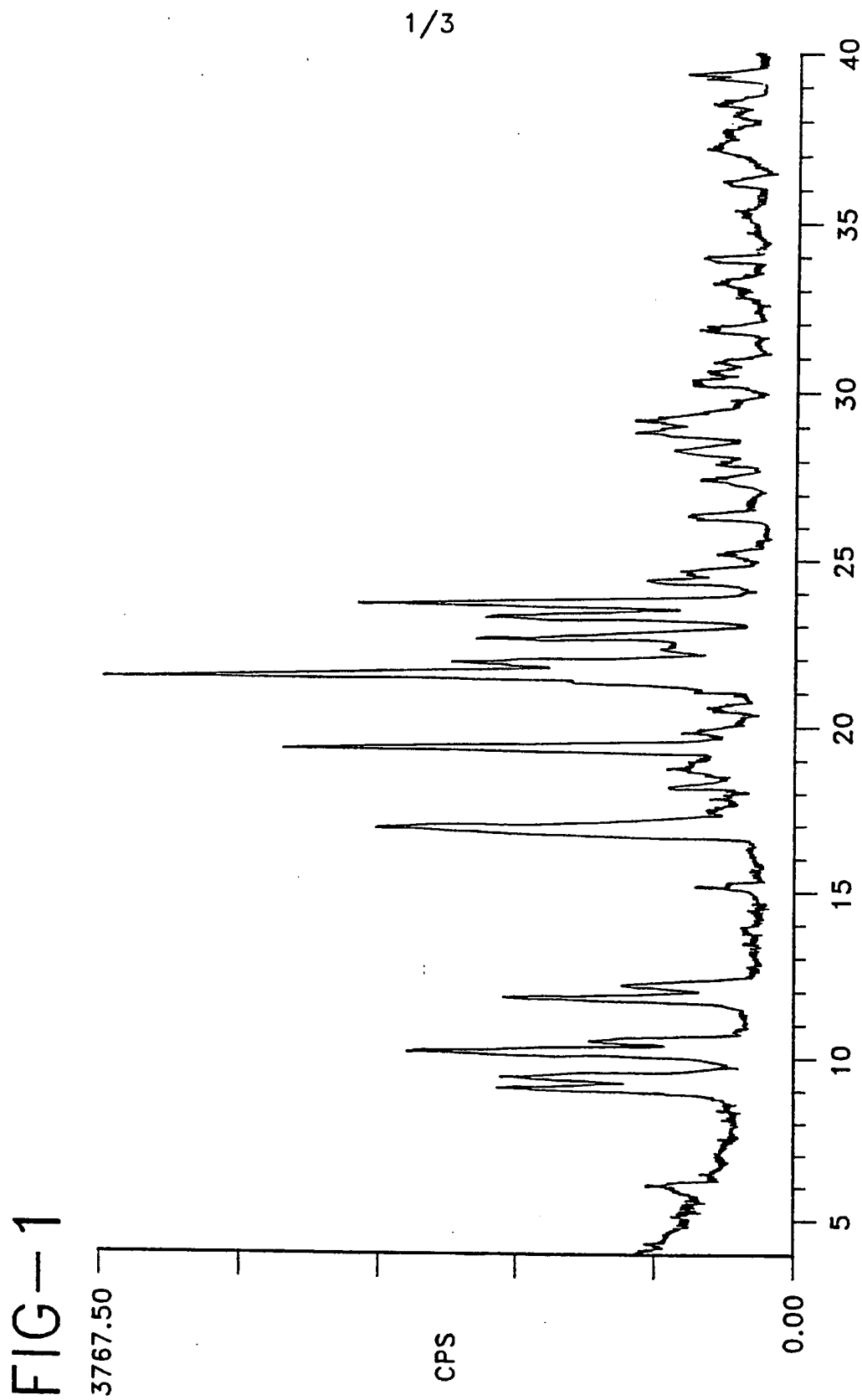
-12-

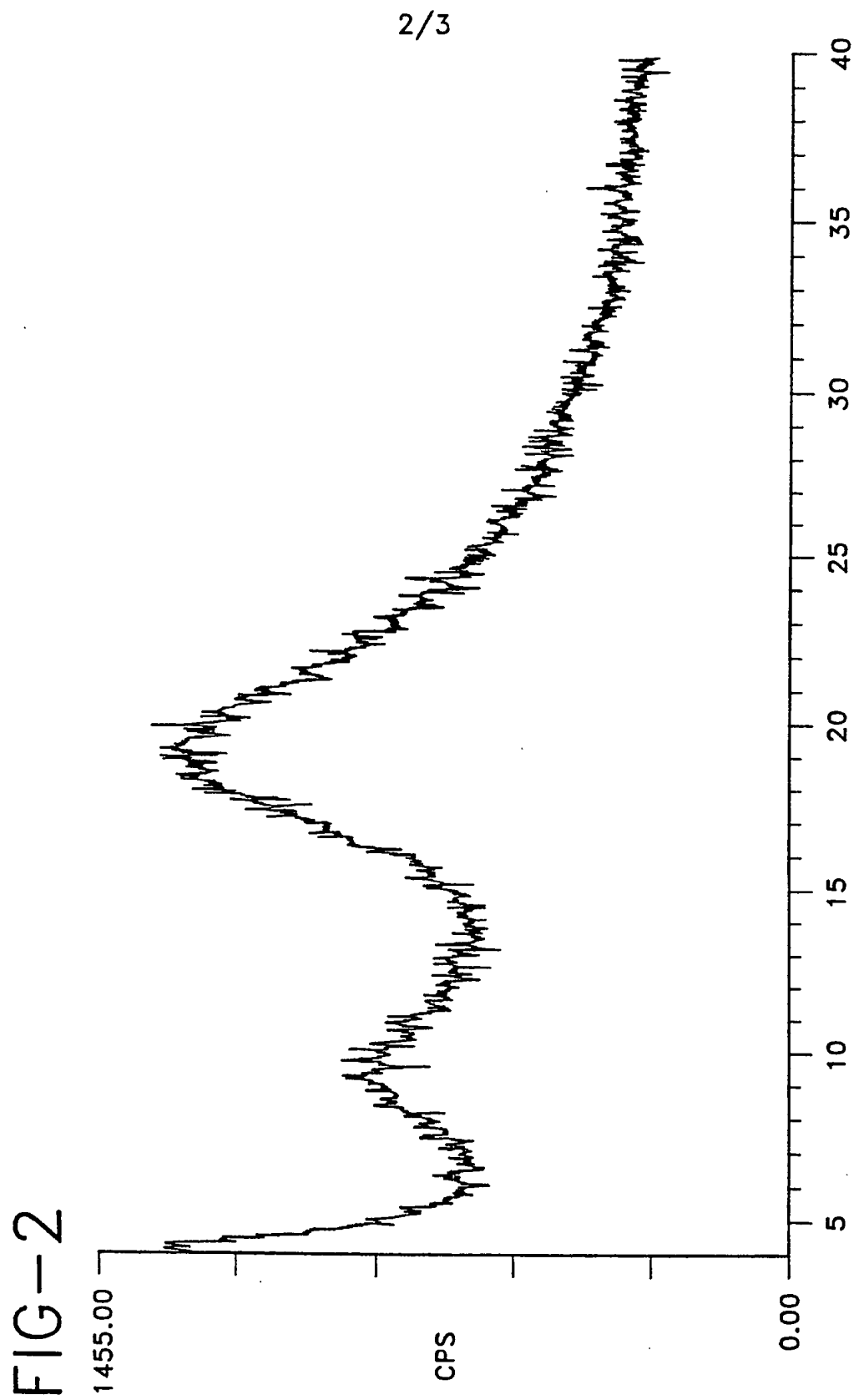
CLAIMS

1. A process for the preparation of amorphous atorvastatin and hydrates thereof which comprises:
 - (a) dissolving crystalline Form I atorvastatin in a non-hydroxylic solvent; and
 - (b) removing the solvent to afford amorphous atorvastatin.
2. A process according to Claim 1 wherein the non-hydroxylic solvent in Step (a) is selected from the group consisting of: tetrahydrofuran, and mixtures of tetrahydrofuran and toluene.
3. A process according to Claim 2 wherein the solvent is a mixture of tetrahydrofuran and toluene.
4. A process according to Claim 1 wherein the solvent in Step (b) is removed by vacuum drying or spray drying.
5. A process according to Claim 4 wherein the solvent in Step (b) is removed by vacuum drying.
6. A process according to Claim 5 wherein vacuum drying is initially carried out at about 20°C to about 40°C and subsequently at about 70°C to about 90°C under vacuum at about 5 mm Hg to about 25 mm Hg.
7. A process according to Claim 6 wherein vacuum drying is initially carried out at about 35°C and subsequently at about 85°C under vacuum at about 5 mm Hg to about 25 mm Hg.

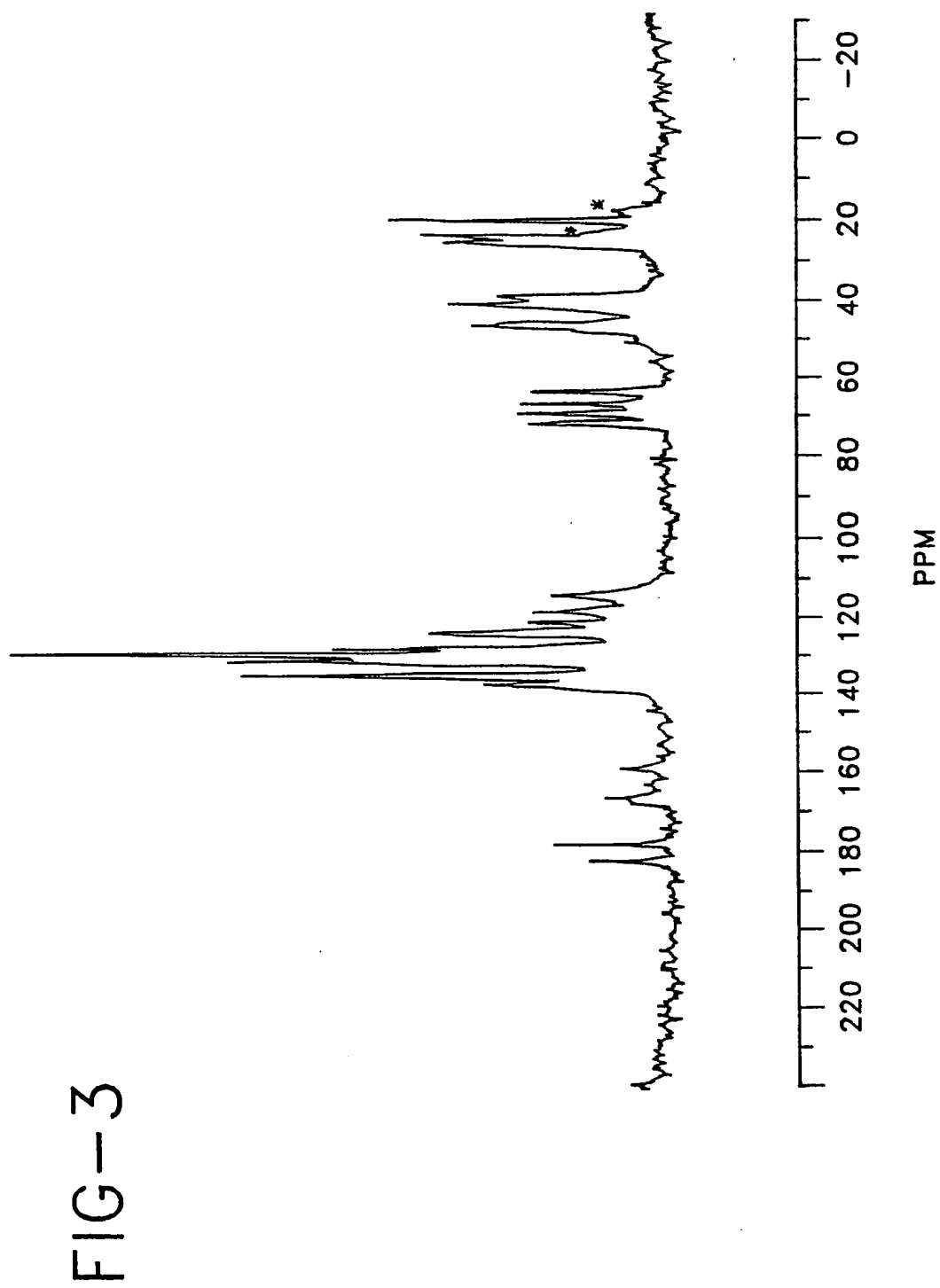
-13-

8. A process according to Claim 5 wherein the material obtained after drying is a brittle foam which is broken up by mechanical agitation.





3/3



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 96/11807

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 20492 (WARNER LAMBERT CO) 15 September 1994 cited in the application see the whole document ---	1-8
A	EP,A,0 409 281 (WARNER LAMBERT CO) 23 January 1991 cited in the application see the whole document ---	1-8
A	EP,A,0 330 172 (WARNER LAMBERT CO) 30 August 1989 cited in the application see the whole document ---	1-8
-/--		

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

23 October 1996

Date of mailing of the international search report

15. 11. 96

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Stellmach, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,89 07598 (WARNER LAMBERT CO) 24 August 1989 cited in the application see the whole document ---	1-8
A	EP,A,0 247 633 (WARNER LAMBERT CO) 2 December 1987 cited in the application see the whole document ---	1-8
A	TETRAHEDRON LETT., vol. 33, no. 17, 1992, OXFORD, pages 2283-2284, XP002016558 BAUMANN,K.L. ET AL.: "The convergent Synthesis of CI-981, an Optically Active, Highly Potent Tissue Selective Inhibitor of HMG-CoA Reductase" see the whole document ---	1-8
A	CHEM.PHARM.BULL., vol. 38, no. 7, 1990, TOKYO, pages 2003-2007, XP002016659 KONNO,T.: "Physical and Chemical Changes of Medicinals in Mixtures with Adsorbents in the Solid State. IV. Study on Reduced- Pressure Mixing for Practical Use of Amorphous Mixtures of Flufenamic Acid" cited in the application see the whole document -----	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No

PCT/US 96/11807

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9420492	15-09-94	US-A- 5298627	29-03-94
		AU-A- 6274294	26-09-94
		CA-A- 2155952	15-09-94
		CZ-A- 9502206	13-12-95
		EP-A- 0687263	20-12-95
		FI-A- 954073	30-08-95
		JP-T- 8507521	13-08-96
		NO-A- 953438	01-11-95
		SK-A- 109095	06-12-95
		US-A- 5342952	30-08-94
		US-A- 5397792	14-03-95
		US-A- 5446054	29-08-95
		US-A- 5470981	28-11-95
		US-A- 5510488	23-04-96
		US-A- 5489691	06-02-96
		US-A- 5489690	06-02-96
EP-A-0409281	23-01-91	AU-B- 628198	10-09-92
		AU-A- 5972490	24-01-91
		CA-A- 2021546	22-01-91
		FI-B- 94339	15-05-95
		JP-A- 3058967	14-03-91
		NO-B- 174709	14-03-94
		NO-B- 176096	24-10-94
		US-A- 5273995	28-12-93
EP-A-0330172	30-08-89	US-A- 5003080	26-03-91
		AT-T- 109777	15-08-94
		AU-B- 634689	25-02-93
		AU-A- 1601792	09-07-92
		AU-B- 635171	11-03-93
		AU-A- 1601892	09-07-92
		AU-A- 3349689	06-09-89
		CA-A- 1330441	28-06-94
		DE-D- 68917336	15-09-94
		DE-T- 68917336	01-12-94
		EP-A- 0448552	02-10-91
		ES-T- 2058356	01-11-94
		FI-B- 94958	15-08-95
		FI-A,B,C 941550	05-04-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/11807

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0330172		IE-B- 63994	28-06-95
		JP-T- 3502798	27-06-91
		NO-B- 177566	03-07-95
		NO-A,B,C 941725	27-09-90
		NO-A,B,C 943057	27-09-90
		NO-A- 951075	27-09-90
		NO-A- 963245	27-09-90
		PT-B- 89774	31-03-94
		US-A- 5245047	14-09-93
		US-A- 5280126	18-01-94
		WO-A- 8907598	24-08-89
		US-A- 5124482	23-06-92
		US-A- 5149837	22-09-92
		US-A- 5216174	01-06-93
		US-A- 5097045	17-03-92

WO-A-8907598	24-08-89	US-A- 5003080	26-03-91
		AT-T- 109777	15-08-94
		AU-B- 634689	25-02-93
		AU-A- 1601792	09-07-92
		AU-B- 635171	11-03-93
		AU-A- 1601892	09-07-92
		AU-A- 3349689	06-09-89
		CA-A- 1330441	28-06-94
		DE-D- 68917336	15-09-94
		DE-T- 68917336	01-12-94
		EP-A- 0330172	30-08-89
		EP-A- 0448552	02-10-91
		ES-T- 2058356	01-11-94
		FI-B- 94958	15-08-95
		FI-A,B,C 941550	05-04-94
		IE-B- 63994	28-06-95
		JP-T- 3502798	27-06-91
		NO-B- 177566	03-07-95
		NO-A,B,C 941725	27-09-90
		NO-A,B,C 943057	27-09-90
		NO-A- 951075	27-09-90
		NO-A- 963245	27-09-90
		PT-B- 89774	31-03-94
		US-A- 5245047	14-09-93

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/11807

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8907598		US-A- 5280126	18-01-94
		US-A- 5124482	23-06-92
		US-A- 5149837	22-09-92
		US-A- 5216174	01-06-93
		US-A- 5097045	17-03-92

EP-A-0247633	02-12-87	US-A- 4681893	21-07-87
		AU-B- 601981	27-09-90
		AU-A- 7315987	03-12-87
		CA-A- 1268768	08-05-90
		FI-C- 88617	10-06-93
		HK-A- 119493	12-11-93
		IE-B- 60014	18-05-94
		JP-B- 7057751	21-06-95
		JP-A- 62289577	16-12-87
		KR-B- 9401006	08-02-94

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